Ernest Overton (1899). Overton had shown that the membrane, comprised largely of fats and lipids, served as a semipermeable osmotic barrier between a cell and its environment; he also had investigated the ability of hundreds of organic solutes to cross cell membranes. Working with sea urchin eggs, Warburg (1910) pinpointed the membrane as the site of respiration by showing that alkaline solutions increased the respiration of sea urchins without altering the alkalinity of the protoplasm, and that fatty acids and organic solvents, which affected membranes, decreased respiration. Warburg (1913b) subsequently investigated the effect of narcotics such as ethyl urethane on respiration, and from this research eventually concluded that it was not the lipids of the membranes that they affected, but solid particles in the protoplasm which turned out to be mitochondria. Even as the details of his account shifted, a constant theme at this stage in Warburg's career was his opposition to the view that soluble enzymes alone were responsible for significant biological processes – he maintained that they operated in context of structured systems (Warburg, 1913a).[42]

It was in this context of emphasizing that enzymes operated in structured systems that Warburg first introduced the term *Atmungsferment* to designate the agent responsible for biological respiration. He viewed it as operating on oxygen, activating it so that it would combine with hydrogen in the substrate undergoing oxidation. Working with Meyerhof, Warburg connected the effect of citric acid and tartaric acid in halting respiration in sea urchin eggs to their ability to chelate (form ring structures with) heavy metals. He concluded "that the oxygen respiration in the egg is an iron catalysis; that the oxygen consumed in the respiratory process is taken up initially by dissolved or absorbed ferrous ions" (Warburg, 1914, pp. 253–4, translated in Fruton, 1972, p. 302). Now Warburg proposed that *Atmungsferment* consisted of ferrous iron adsorbed onto the membranes of the cell. Warburg also developed model systems of activated charcoal or pyrolised (heat-transformed) blood in which to study the reaction.

[42] Warburg also criticized Buchner's characterization of zymase as a soluble enzyme. He interpreted the slowing of fermentation in cell-free extracts identified by Harden and Young as indicating the destruction of the membrane which was critical to the normal operation of the ferment. At this point, Warburg insisted that both cell structure and enzymes (for him, ferments) were required: "The question always comes to this: cell action or ferment action? Structure action or ferment action? I hope I have demonstrated to you today that there is no dichotomy here at all: both ferment chemists and biologists are right. The acceleration of energy-producing reactions in cells is a ferment action *and* a structure action; it is not that both ferments *and* structure accelerate, but that *structure accelerates ferment action*" (1913a, pp. 20–1, translated in Kohler, 1973, pp. 189–90).